Mitral valve prolapse: The Merchant of Venice or Much Ado About Nothing?

Mitral valve prolapse has entered its age of maturity, with a lifetime that spans almost four decades since Barlow et al. first demonstrated the association of mid-systolic clicks and late systolic murmurs with systolic aneurysmal billowing of the posterior mitral leaflet into the left atrium. In the intervening years, mitral valve prolapse has been associated with a wide spectrum of definitions and a variety of terms. Through this initial haze of terminology, it has now been clarified that mitral valve prolapse is not a single entity but a spectrum of abnormalities with a variety of clinical, echocardiographic and pathological features. Morphologically, the extremes of this spectrum are normal-appearing mitral leaflets that billow mildly into the left atrium and redundant leaflets resulting from marked myxomatous proliferation of the spongiosa component of the valve and elongation of the cordal apparatus. Mild leaflet displacement may not be accompanied by mitral regurgitation whereas marked billowing with loss of systolic apposition can result in grave regurgitation.

Mitral valve prolapse has a strong hereditary component and is most frequently a primary condition. However, it is often associated with many disorders and the readily emerging question is, as Malcom expressed it, to what extent are these associations a casual coincidence, a common link, or an expression of a fundamental genetic disturbance. Commonly associated conditions are heritable disorders of connective tissue, such as the Marfan syndrome, the Ehlers–Danlos syndrome, osteogenesis imperfecta, adult polycystic kidney disease and pseu-

As regards clinical presentation, the majority of patients are asymptomatic. Symptoms may be related directly to mitral valve dysfunction. Boudoulas et al. have described the mitral valve prolapse syndrome, in reference to a subset of patients whose cardiac and non-cardiac symptoms cannot be explained by mitral valve abnormalities and dysfunction alone. Such patients present with a characteristic non-ejection click and a variety of non-specific symptoms, such as fatigue, palpitations, chest pain, postural orthostasis, syncope or presyncope, and neuropsychiatric symptoms. These symptoms may result from neuroendocrine or autonomic dysfunction, and impairment of left atrial function might have a contributory role. In addition, patients may present with a variety of symptoms originating from both valvular and autonomic dysfunction.

The most important aspect of a disease is its clinical importance and this can be determined following three steps that should be taken carefully and are largely interrelated. First, the true prevalence of the disease should be defined. Second, the true risk associations should be determined with flawless methodology. Finally, diagnostic criteria should categorize the patients according to the severity of the risk. Unfortunately, uncertainty regarding the true prevalence of mitral valve prolapse on the one hand and the serious complications that have been ascribed to the abnormality on the other, constitute the double-faceted confusion with which the medical community has been confronted. This confusion has often led to undue labelling and ‘overtreatment’ of mostly young ‘patients’, with important psychological consequences and socioeconomic implications.

Starting with a ‘flexible’ definition such as that of ‘mitral valve prolapse’, it is apparent that there are inherent difficulties in pursuing the determination of its true prevalence. In this environment, the crucial role of diagnostic techniques is to minimize false-positive results. This can be achieved through evolution and refinement of diagnostic techniques and increasing knowledge regarding disease mechanisms. Diagnostic tools used in the diagnosis of the
abnormality have included auscultation, M-mode, two dimensional and transoesophageal echocardiography, left ventriculography and direct histopathological inspection of the mitral valve apparatus. Based on these diagnostic techniques, many criteria both major and minor have been proposed and some non-specific findings have been associated with the entity[9].

Although these criteria may help orient the clinician towards the disorder, they do not clear up the confusion as to what is its real prevalence. The prevalence has been reported to range from 5 to 10% in the general population and even higher among young women[10–11]. Echocardiography has been an invaluable diagnostic tool, but at the same time has undoubtedly catalyzed over-diagnosis. Given that the generic definition of prolapse is displacement of the mitral valve leaflets relative to their surrounding tissues, M-mode echocardiography has an obvious disadvantage: it does not display the leaflets in relation to their surrounding annular attachments. Moreover, images obtained are strongly dependent on the orientation of the transducer. Two-dimensional echocardiographic views overcome such limitations, but nevertheless, the non-planar ‘saddle shape’ of normal mitral leaflets that has been documented in three-dimensional studies[12] can give the impression of prolapsing leaflets in certain echocardiographic views. Finally, an additional factor that has contributed to the reportedly high prevalence is selection bias, an inherent limitation of the numerous referral-based studies.

Volunteers responding to an advertisement or agreeing to participate after random selection, do not represent a typical community sample since they are more health-concerned, either due to history of a heart murmur or positive family history. In a recent study, Freed and colleagues[13] used rigorous echocardiographic criteria for the diagnosis of mitral valve prolapse in an unselected, community-based sample of ambulatory patients. Based on these diagnostic criteria and on such a population selection, prevalence was lower than previously reported. Classic mitral valve prolapse was defined as superior displacement of the mitral leaflets, by more than 2 mm during systole, with maximal leaflet thickness of at least 5 mm during diastasis; non-classic prolapse was defined as displacement by more than 2 mm, with a maximal thickness of less than 5 mm. Using these criteria in 3491 screened subjects, 2.4% had mitral valve prolapse, with 1.3% fulfilling the criteria according to the classic definition and 1.1% according to the non-classic definition.

Although mitral valve prolapse is generally considered a benign condition, serious complications have been ascribed to it, including infective endocarditis, severe mitral regurgitation needing surgical intervention, heart failure, cerebral and coronary embolic events, arrhythmias and even sudden death[14,15]. However, it appears that the actual risk, although not negligible in specific subgroups, is less compared to that of early reports. Explanations for this discrepancy can be sought either in the referral bias or in the considerable number of retrospective identifications of mitral valve prolapse among patients with complications in some of these early studies. Zuppiroli et al.[6] in an 8 year plus follow-up study reported a low (1% per year) overall rate of fatal and non-fatal complications. Progressive mitral regurgitation is the most frequent complication and the risk is greater in patients with both murmurs and clicks than in those with an isolated click.

The incidence of infective endocarditis also rises in the presence of a murmur, whereas patients with only a mid-systolic click are at very low risk[16]. It appears that the risk of sudden death increases slightly in patients with severe valvular deformities or severe mitral regurgitation[4,17,18]. The association between stroke and mitral valve prolapse has been controversial. In a recent study, Gilson et al.[19], using highly specific echocardiographic criteria for mitral valve prolapse could not demonstrate an association in young people, although a small association cannot be ruled out. Valve redundancy appears to be a significant factor predisposing to adverse effects[17,20]. According to Zuppiroli et al.[6] the risk for complications is higher in men, in subjects aged over 45 years, and in those with evidence of significant mitral regurgitation (holosystolic murmur and left-sided chamber enlargement).

In light of the new data that have emerged during recent years, management of mitral valve prolapse can be approached more rationally (Fig. 1). Nishimura and McGoon[21] have suggested that the hallmarks of this approach should be the echocardiographic categorization of patients according to rigorous criteria that should be adopted by all laboratories. Indeed, patients with mild bulging of morphologically normal-appearing leaflets have a minor, or no, risk of complications. In the absence of a systolic murmur, reassurance and follow-up at moderate intervals with clinical evaluation and echocardiography is adequate[41]. Antibiotic prophylaxis against infective endocarditis is optional and may be unnecessary. In the presence of a systolic murmur, antibiotic prophylaxis is justified and follow-up should be frequent (e.g. every 2 years).

Patients with redundant and thickened leaflets are considered as having a primary form of the disease and the mainstay of treatment is close patient
Mitral valve prolapse-treatment

2-D echocardiography using standardized, rigorous criteria

risk

Normal variant form
Systolic murmur

- Reassurance
- Antibiotic prophylaxis optional
- Follow-up moderate (5 years)

Primary form

- Antibiotic prophylaxis
- Follow-up more frequent (2 years)

Figure 1 A logical approach in the management of mitral valve prolapse.

observation. Clinical evaluation and echocardiographic follow-up should be performed every year or earlier if substantial mitral regurgitation is present. Prophylaxis against infective endocarditis is mandatory. In the presence of mitral regurgitation, afterload should be optimized and development of resultant left ventricular failure should be treated, as in other patients, with severe mitral regurgitation. Reconstructive surgery without valve replacement is increasingly performed with very good immediate results (approximately 2% operative mortality) and favourable long-term outcome[22].

These favourable results are an incentive for early surgery before ventricular dysfunction occurs. Beta-adrenoreceptors are useful in the management of palpitations or associated myocardial ischaemia. Severe arrhythmias may need further electrophysiological investigation. Finally, it should be emphasized that despite the risk of complications in specific patient subgroups, the majority of patients remain asymptomatic throughout their lives. Follow-up assessment and reassurance are all that is needed for such patients, who do not deserve being labelled for their entire lives as having a potentially malignant disease.

Does the mitral valve prolapse syndrome mercilessly claim the life of its patients, like Shylock, in the Merchant of Venice, who claimed the heart of Portia’s lover? Or has too much fuss been made and too many literature pages been wasted on something almost non-existent? The truth, as with most things in real life, lies somewhere in the middle. Prudence in diagnosis, based on rigorous criteria and robust epidemiological data, will define the true prevalence of the disease and outline the risks. Modern technology and maturity is on our side.

C. STEFANADIS
P. TOUTOUZAS
Department of Cardiology,
Hippokration Hospital,
Athens Medical School,
Athens, Greece

References


